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Pseudo-phosphorylation at AT8 epitopes regulates the tau truncation at aspartate 421

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Abstract

Tau pathology in Alzheimer's disease (AD) includes hyperphosphorylation and truncation of tau. Phosphorylation at S422 is found to suppress truncation of tau at D421 that leading to the generation of ΔTau. However, the interrelation between hyperphosphorylation and generation of ΔTau in AD remains elusive. In current study, staurosporine (Stau) induced ΔTau generation by caspases in SH-SY5Y cells with tau overexpression was found to be accompanied by a dramatic dephosphorylation at S422 and the epitope of the diagnostic antibody AT8 (S199+S202+T205), but a moderate dephosphorylation of PHF1 (S396+S404) epitope. Therefore, to explore the effect of AT8 epitope on tau truncation, the residues in AT8 epitope were mutated to produce "pseudo-phosphorylated" (AT8E) or "pseudo-unphosphorylated" (AT8A) tau constructs. With Stau treatment, the generation of ΔTau from tau-AT8E was significantly attenuated comparing with that from tau-AT8A, which was S422-independent in that addition of S422A mutation still preserved this effect. Interestingly, this modulatory effect was able to be reversed by addition of PHF1E mutation. Moreover, treating the crude tau extracts with recombinant caspase-3 *in vitro*, also showed that ΔTau level was suppressed by AT8E, and potentiated by AT8E+PHF1E. The